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Etoricoxib

Deborah J. Cochrane, Blair Jarvis and *Gillian M. Keating*
Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Etoricoxib is a cyclo-oxygenase (COX)-2-selective NSAID with a higher COX-1 to COX-2 selectivity ratio than the other COX-2-selective NSAIDs rofecoxib, valdecoxib or celecoxib.

▲ In patients with rheumatoid arthritis, improvements in tender and swollen joint counts and patient and investigator global assessment of disease activity were significantly greater in etoricoxib than in placebo recipients in two studies. Etoricoxib was also significantly more effective than naproxen in one of these studies.

▲ In patients with osteoarthritis of the hip or knee, etoricoxib was significantly more effective than placebo and had similar efficacy to naproxen with regards to improvements in pain and physical function scores and patient global assessment of disease status scores in two studies. Etoricoxib had similar efficacy to diclofenac in patients with osteoarthritis of the knee.

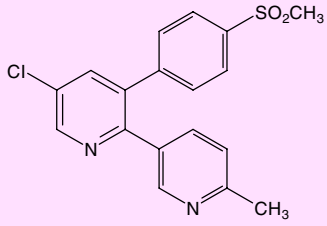
▲ Single-dose etoricoxib relieved pain in patients with postoperative dental pain in two studies. Similar scores assessing total pain relief over 8 hours (TOPAR8) were reported in etoricoxib and naproxen sodium or ibuprofen recipients, and higher TOPAR8 scores were reported with etoricoxib than with paracetamol (acetaminophen)/codeine.

▲ Pain relief was significantly better with etoricoxib than placebo in two studies in patients with chronic low back pain.

▲ Etoricoxib had similar efficacy to indomethacin in a study in patients with acute gout, and single-dose etoricoxib had similar efficacy to naproxen sodium in a study in women with primary dysmenorrhoea.

▲ Compared with non-COX-selective NSAIDs, etoricoxib was associated with significantly fewer upper gastrointestinal (GI) perforations, ulcers or bleeds, and was significantly less likely to result in treatment discontinuation because of NSAID-type GI symptoms or any GI symptoms.

Features and properties of etoricoxib (MK663)	
Indications	
Rheumatoid arthritis, osteoarthritis, acute gout, chronic musculoskeletal pain (including chronic low back pain), postoperative dental pain and primary dysmenorrhoea	
Mechanism of action	
Cyclo-oxygenase (COX)-2-selective NSAID	
Dosage and administration	
Recommended dosage	60, 90 or 120 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (120mg once daily at steady state)	
Peak plasma concentration	3.6 mg/L
Time to peak plasma concentration	≈1h
Area under the plasma concentration-time curve from 0 to 24h	37.8 mg • h/L
Mean oral bioavailability	≈100%
Route of elimination	Hepatic
Elimination half-life	≈22h
Adverse events	
Generally well tolerated with significantly fewer upper gastrointestinal perforations, ulcers and bleeds than non-COX-selective NSAIDs.	



Etoricoxib

NSAIDs have been used for decades for the treatment of pain and inflammation. Conventional NSAIDs are very effective in treating pain; however, they have a poor tolerability profile as they are associated with an increased risk of damage to the gastrointestinal (GI) tract.[1]

NSAIDs affect the arachidonic acid cascade by inhibiting cyclo-oxygenase (COX), thereby attenuating prostaglandin and thromboxane production. COX exists as at least two isoforms;[2] COX-1 is the constitutive form and COX-2 is inducible. The products of COX-1 activity are involved in platelet function, regulation of renal haemodynamics and electrolyte balance, and protection of the GI mucosa. COX-2 is responsible for the production of prostaglandins that mediate inflammation and pain, and it is primarily the inhibition of COX-2 that results in the analgesic and anti-inflammatory effects of NSAIDs. However, in reality this may be a somewhat simplistic view, as both COX isoforms appear to have wider physiological activity than originally thought.[3]

COX-2-selective NSAIDs should, in theory, be as effective as nonselective NSAIDs, but lack the GI tolerability concerns associated with COX-1 inhibition. Consistent with this expectation, available COX-2-selective NSAIDs have similar efficacy to, but are better tolerated than, conventional NSAIDs when used in the treatment of rheumatoid arthritis, osteoarthritis and acute pain.[4,5]

Etoricoxib, the subject of this review, is a COX-2-selective NSAID used in the treatment of rheumatoid arthritis, osteoarthritis, postoperative dental pain, chronic low back pain, acute gout and primary dysmenorrhoea.

1. Pharmacodynamic Profile

In Vitro

- Etoricoxib selectively inhibited COX-2 in an *in vitro* human blood assay.[6] The concentration required to inhibit COX-2 activity by 50% (IC_{50}) was 1.1 μmol/L, as indicated by lipopolysaccharide (LPS)-induced prostaglandin E_2 (PGE_2) synthesis, compared with 116 μmol/L for COX-1, as indicated by serum thromboxane B2 generation after blood clotting.
- The COX-1 to COX-2 selectivity ratio was higher for etoricoxib than for other COX-2-selective inhibitors such as rofecoxib, valdecoxib and celecoxib (see figure 1).[6] In the U937 microsomal assay (the most sensitive indicator of COX-1 inhibition), IC_{50} values were 12.1 μmol/L for etoricoxib, 2.0 μmol/L for rofecoxib, 0.25 μmol/L for valdecoxib and 0.052 μmol/L for celecoxib.[6]
- Similar results were seen in another *in vitro* study in which the COX-1 to COX-2 IC_{50} ratio was 323 for etoricoxib, 267 for rofecoxib, 61 for valdecoxib and 30 for celecoxib, assessed using a human whole blood assay.[7]
- Etoricoxib is the COX-2 inhibitor least likely to interfere with the antiplatelet effect of aspirin (mediated via the irreversible inactivation of COX-1).[8] The concentration of NSAID required to antagonise by 50% the inactivation of platelet COX-1 by aspirin 10 μmol/L was 0.048, 0.21, 0.7, 5.3 and 19 μmol/L for ibuprofen, celecoxib, valdecoxib, rofecoxib and etoricoxib, respectively, in an *in vitro* study.

In Human Volunteers

- The maximum mean inhibition of LPS-induced PGE2 synthesis was dose-proportional after a single dose of etoricoxib 5 to 500mg and after etoricoxib 25 to 150 mg/day for 9 days, in an *ex vivo* assay, using blood samples from healthy volunteers.[9] PGE2 levels were significantly lower

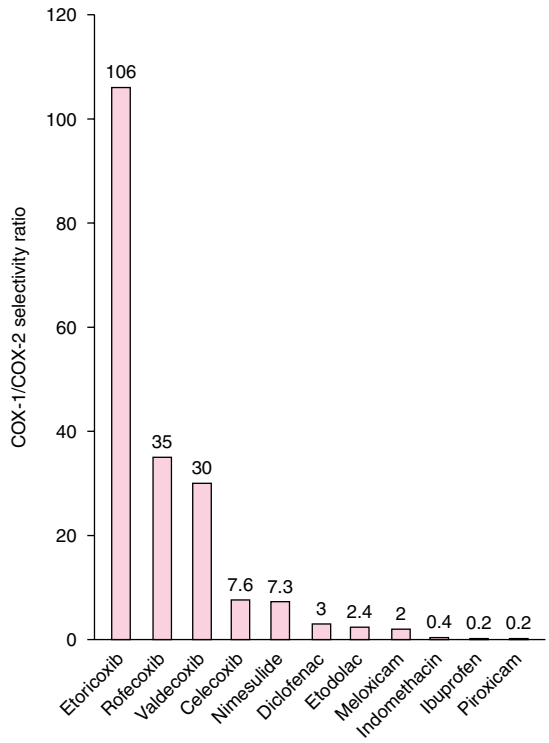


Fig. 1. Cyclo-oxygenase (COX)-1 to COX-2 selectivity ratio of various COX-2 selective inhibitors.[6] The concentration required to inhibit COX-1 and COX-2 activity by 50% was assessed in an *in vitro* human whole blood assay.

compared with baseline when assessed 24 hours postdose after repeated administration (p value not stated).

• Etoricoxib did not affect the antiplatelet effects of low-dose aspirin.[10] Twelve volunteers were randomised in a double-blind study to etoricoxib 120 mg/day or placebo for 12 days; nonblind aspirin 81 mg/day was given from day 6 to 12. Inhibition of *ex vivo*-generated thromboxane and arachidonic acid-induced platelet aggregation was similar in both groups at baseline and at day 12.

• Etoricoxib did not increase faecal blood loss in healthy volunteers who were injected with ^{51}Cr-labelled red blood cells.[11] Sixty-two healthy volunteers in a double-blind study were randomised to etoricoxib 120mg once daily, ibuprofen 800mg three times daily or placebo for 28 days. Daily faecal blood loss, as assessed by the presence of ^{51}Cr in stool samples, was similar in recipients of etoricoxib or placebo. In contrast, mean faecal blood loss was approximately 3-fold higher in ibuprofen recipients at endpoint.

2. Pharmacokinetic Profile

Absorption and Distribution

• Etoricoxib is rapidly absorbed with a mean oral bioavailability of ≈100%.[12] At steady state (reached within 7 days), the mean peak plasma concentration (C_{max}) of etoricoxib of 3.6 mg/L was reached after ≈1 hour with once-daily administration of etoricoxib 120mg in fasted adults.[12] The mean area under the plasma concentration-time curve (AUC) was 37.8 mg • h/L. No clinically significant alteration in the extent or rate of absorption of etoricoxib 120mg was reported when the drug was administered with a standard meal.[12]

• In studies in healthy volunteers, there was a linear relationship between dose (5 to 150mg) and the C_{max}[9,13] and AUC[13,14] of etoricoxib (after both single and repeated administration).

• Etoricoxib has a volume of distribution at steady-state of ≈120L and is ≈92% plasma protein bound.[12]

Metabolism and Elimination

• An *in vitro* study in human liver microsomes indicated that etoricoxib undergoes extensive metabolism. The presence of the major metabolite, a 6′-hydroxymethyl derivative of etoricoxib, is accounted for by cytochrome P450 (CYP) 3A4 activity. CYP2D6, CYP2C9, CYP1A2 and possibly CYP2C19 may play a minor role in the metabolism of the drug.[15]

• After administration of a single dose of radiolabelled etoricoxib 25mg, 70 and 20% of radioactivity was recovered in the urine and faeces, respectively (<2% was recovered as unchanged etoricoxib).[12]

• Etoricoxib had an elimination half-life of ≈22 hours after administration of single doses (5 to 120mg) to 12 healthy volunteers in a nonblind,

crossover study.[13] After intravenous administration of etoricoxib 25mg, the plasma clearance was ≈3 L/h.[12]

Special Patient Populations

• The pharmacokinetics of etoricoxib are similar in men and women, and in the young and the elderly (patients aged ≥65 years).[12] Moreover, the pharmacokinetics of etoricoxib in adults (90mg once daily) were similar to those in adolescents aged 12 to 17 years with bodyweights of 40 to 60kg (60mg once daily) or >60kg (90mg once daily) who received etoricoxib.[12] The pharmacokinetics of etoricoxib in patients aged <12 years have not been studied.[12]

• The pharmacokinetics of a single dose of etoricoxib 120mg were similar in patients with moderate-to-severe renal dysfunction or end-stage renal disease requiring haemodialysis to those in healthy volunteers.[12]

• Following administration of etoricoxib 60mg once daily, the mean AUC was ≈16% higher in patients with mild hepatic dysfunction (Child-Pugh score 5 to 6) than in healthy volunteers. In patients with moderate hepatic dysfunction (Child-Pugh score 7 to 9) who received etoricoxib 60mg every other day, the mean AUC was similar to that reported in healthy volunteers who received etoricoxib 60mg once daily. There are no data examining the use of etoricoxib in patients with severe hepatic dysfunction (Child-Pugh score >9).[12]

Potential Drug Interactions

• Etoricoxib did not significantly inhibit or induce CYP3A4 *in vitro*, and is therefore unlikely to affect the pharmacokinetics of other drugs metabolised by CYP3A4.[16] Coadministration of ketoconazole 400mg once daily for 11 days increased the AUC of a single dose of etoricoxib 60mg by 43%, but this was not considered clinically important.[12] Coadministration of rifampicin (rifampin) and etoricoxib was associated with a reduction in the plasma etoricoxib concentration of 65%.[12]

• Coadministration (either concomitantly or at 12-hour intervals) of etoricoxib 120mg and ethinylestradiol/norethindrone (norethisterone) 35μg/0.5 to 1mg for 21 days was associated with an increase in the steady-state AUC_{24h} of ethinylestradiol of 50 to 60%. In general, the increase in norethindrone concentrations was not considered clinically relevant.[12]

• Coadministration of etoricoxib 120mg once daily for 10 days did not alter the renal elimination or steady-state AUC_{24h} of digoxin in healthy volunteers.[12] There was an increase in the C_{max} of digoxin of ≈33%; thus, patients considered at high risk of digoxin toxicity should be monitored when these drugs are coadministered.

• Coadministration of an antacid and etoricoxib resulted in minimal alterations (i.e. <10%) in the AUC of etoricoxib in 12 healthy volunteers.[17] C_{max} values were reduced by <25% with administration of an antacid plus etoricoxib, compared with etoricoxib alone.

• The pharmacokinetics of prednisolone and prednisone were not affected by coadministration of etoricoxib 120 mg/day in 12 healthy volunteers in a multiple-dose, crossover study.[18]

• In two studies, administration of once-daily etoricoxib 60 or 90mg (doses recommended in the treatment of chronic conditions such as osteoarthritis and rheumatoid arthritis) for 7 days did not alter the AUC or renal clearance of methotrexate in patients with rheumatoid arthritis receiving methotrexate 7.5 to 20mg once weekly.[12] Similarly, once-daily etoricoxib 120mg did not affect the AUC or renal clearance of methotrexate in one of the studies. However, in the second study, administration of etoricoxib 120mg once daily was associated with a 28% increase in methotrexate AUC and a 13% reduction in the renal clearance of methotrexate. Thus, patients receiving both drugs should undergo adequate monitoring for methotrexate-associated toxicity.

• Administration of etoricoxib 120mg once daily in patients receiving long-term warfarin therapy was associated with a 13% increase in the interna-

tional normalised ratio (INR).[12] Thus, patients receiving warfarin and etoricoxib should have their INR closely monitored, especially after etoricoxib therapy is started or the etoricoxib dosage is changed.

3. Therapeutic Trials

The therapeutic efficacy of etoricoxib has been evaluated in randomised controlled trials in adults with rheumatoid arthritis,[19-21] osteoarthritis,[22-24] postoperative dental pain,[25,26] chronic low back pain,[27,28] acute gout,[29] primary dysmenorrhoea[30] and haemophilic arthropathy.[31] All but one[30] of these studies were parallel in design and all but five[20,21,23,24,29] are available only as abstracts and/or posters. Some of the studies compared etoricoxib with an active comparator.[20-26,29,30]

In Patients with Rheumatoid Arthritis

The efficacy of etoricoxib in patients with rheumatoid arthritis was studied in three multicentre, placebo-controlled trials. One double-blind study compared different doses of etoricoxib with placebo[19] and two double-blind studies compared etoricoxib 90 mg/day with naproxen 500mg twice daily.[20,21] In the 8-week dose-ranging study, 581 patients were randomised to once-daily etoricoxib 10mg (n = 78), 60mg (n = 126), 90mg (n = 134) or 120mg (n = 120) or placebo (n = 123).[19] The active-comparator studies were conducted in 816[20] and 891[21] patients who were randomised to receive 12 weeks' therapy with etoricoxib 90mg once daily (n = 323[20] or 353[21]), naproxen 500mg twice daily (n = 170[20] or 181[21]) or placebo (n = 323[20] or 357[21]).

The primary endpoints in all three studies[19-21] were the changes from baseline in patient [assessed using 100mm visual analogue scales (VAS)] and investigator (assessed using a 5-point Likert scale) global assessments of disease activity and tender and swollen joint counts. In the active-comparator studies,[20,21] key secondary endpoints included the percentage of patients who achieved a 20% improvement in American College of Rheumatology criteria (ACR20) and who completed the study, and the improvements from baseline in patient global assessment of pain (assessed using 100mm VAS scores) and Health Assessment Questionnaire (HAQ) disability scale scores. Health-related quality of life was also assessed in one active-comparator study using Medical Outcomes Trust Short Form (SF)-36 domain (physical functioning, role-physical, pain, general health perceptions, mental health, role-emotional, social functioning and vitality) and physical and mental component summary scores (assessed on a 0- to 100-point scale where higher scores indicate better quality of life).[32]

- In the dose-ranging study, etoricoxib was more effective than placebo; etoricoxib 90 and 120 mg/day showed similar therapeutic benefits. The differences between placebo recipients and recipients of etoricoxib 90 mg/day (–9.41mm) or 120 mg/day (–9.15mm) in the least squares mean change from baseline in patient global assessment of disease activity scores significantly favoured recipients of active treatment ($p < 0.05$); response was averaged over weeks 2 to 8. Significantly fewer ($p < 0.05$) patients receiving once-daily etoricoxib 60 (2%), 90 (2%) or 120mg (3%) than those receiving placebo (9%) discontinued the study because of lack of efficacy.[19]

- In one of the active-comparator studies, etoricoxib 90 mg/day was more effective than naproxen 500mg twice daily as assessed by all primary endpoints.[20] Differences between etoricoxib and naproxen for the least squares mean change from baseline were –5.5mm for patient global assessment of disease activity ($p < 0.01$), –0.28 for investigator global assessment of disease activity ($p < 0.01$), –3.4 for the tender joint count ($p < 0.01$) and –1.5 for the swollen joint count ($p < 0.05$). Differences between etoricoxib and placebo recipients for the least squares mean change from baseline in the corresponding parameters were –17.0, –0.63, –6.3 and –3.3 (all $p < 0.01$).

- Etoricoxib recipients were significantly more likely to achieve an ACR20 response and complete

the study than naproxen ($p < 0.01$) or placebo ($p < 0.01$) recipients [see figure 2].[20] In addition, patient global assessment of pain reflected significantly better ($p < 0.01$) outcomes in patients who received etoricoxib compared with patients who received naproxen or placebo (least squares mean change of –27.2 *vs* –20.5 and –11.4mm).[20]

• Further analysis[33] of this study[20] revealed that functional ability improved to a greater extent in etoricoxib compared with placebo recipients; scores for all eight subdomains of the HAQ (dressing and grooming, arising, walking, gripping, reaching, hygiene, eating and activities of daily living) were significantly better ($p < 0.001$) in etoricoxib than in placebo recipients. In addition, for all 20 questions within the eight subdomains, etoricoxib recipients performed significantly better than placebo recipients ($p < 0.002$). Moreover, etoricoxib recipients achieved significantly better ($p < 0.05$) scores than naproxen recipients in all subdomains but two (hygiene and eating).

• Improvements from baseline in quality of life were greater in etoricoxib recipients than in naproxen or placebo recipients.[32] After 12 weeks' therapy, the differences between etoricoxib and placebo recipients in changes from baseline in all eight SF-36 domain scores significantly favoured etoricoxib recipients (+2.6 to +18.2; $p \leq 0.02$ *vs* placebo). Similarly, the between-treatment difference in the improvement in physical (+5.4) and mental (+2.0) component summary scores significantly favoured etoricoxib recipients ($p \leq 0.004$ *vs* placebo). Moreover, significantly greater improvements in domain scores (except for mental health, role-emotional and vitality scores) and in the physical component summary score were reported in etoricoxib compared with naproxen recipients ($p < 0.05$).

• In the other active-comparator study,[21] etoricoxib recipients had a similar treatment response to naproxen recipients: differences between etoricoxib and naproxen for the least squares mean change from baseline in the patient and investigator global assessments of disease activity and tender and swollen joint counts (+0.09, +0.08, –0.26 and –0.03, respectively) were not statistically significant. With regards to the primary and key secondary endpoints, the differences between active treatment and placebo recipients in the least squares mean changes from baseline were significant ($p < 0.05$). An ACR20 response was seen in 58.7, 57.5 and 40.9% of etoricoxib, naproxen and placebo recipients, respectively ($p < 0.001$ *vs* placebo).

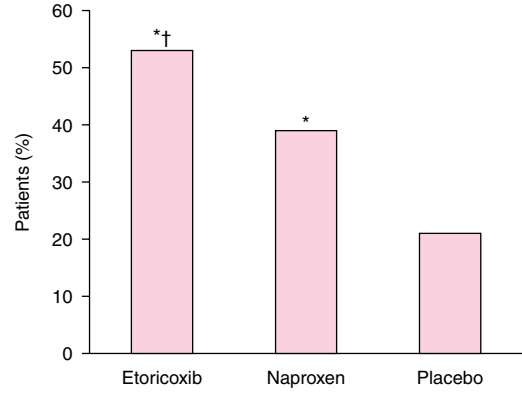


Fig. 2. Percentage of patients who achieved a 20% improvement in American College of Rheumatology criteria and completed the trial. 816 patients with rheumatoid arthritis were randomised in this multicentre, double-blind study to receive etoricoxib 90mg once daily, naproxen 500mg twice daily or placebo for 12 weeks (448 patients completed the trial).[20] * $p < 0.01$ *vs* placebo; † $p < 0.01$ *vs* naproxen.

In Patients with Osteoarthritis

Three multicentre, placebo-controlled trials examined the efficacy of etoricoxib in patients with osteoarthritis. A two-part, double-blind, dose-ranging study included 617 patients with osteoarthritis of the knee.[23] In the first part, patients were randomised to 6 weeks of once-daily etoricoxib 5mg (n = 117), 10mg (n = 114), 30mg (n = 102), 60mg (n = 112) or 90mg (n = 112) or placebo (n = 60). In the second part, patients received once-daily etoricoxib 30mg (n = 198), 60mg (n = 102) or 90mg (n = 148) or diclofenac 50mg three times daily (n = 102) for 8 weeks. Two studies comparing etoricoxib with naproxen enrolled 501[24] and

496[22] patients with osteoarthritis of the hip or knee who had increased pain after withdrawal of NSAIDs,[22,24] paracetamol (acetaminophen)[22] or COX-2 inhibitors.[24] In both studies, patients were randomised to receive etoricoxib 60mg once daily (n = 224[24] and 222[22]), naproxen 500mg twice daily (n = 221[24] and 218[22]) or placebo (n = 56[24] and 56[22]). After 12 weeks of therapy, recipients of etoricoxib or naproxen continued their allotted therapy for another 40 weeks (a total of 52 weeks); placebo recipients were switched to 40 weeks' treatment with either etoricoxib 60 mg/day or naproxen 1 g/day according to a randomisation procedure conducted at baseline.

The three primary endpoints in the dose-ranging study[23] were the changes from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, patient assessment of response to therapy and investigator assessment of disease status scores. The endpoints utilised in the active-comparator studies were the changes from baseline in WOMAC pain and physical function subscale scores and the patient global assessment of disease status score.[22,24] The WOMAC subscales assessed response using a 100mm VAS.

Combined data from the two studies comparing etorixocib with naproxen[22,24] have been examined in five additional analyses.[34-38]

• In the first part of the dose-ranging study, all doses of etoricoxib were significantly more effective than placebo ($p < 0.05$), as measured by the between-group difference in the least squares mean change from baseline in WOMAC pain subscale scores (see figure 3); response was averaged over weeks 2 to 6.[23]

• Improvements in primary outcome measures were sustained throughout the trial in patients who received etoricoxib 30, 60 or 90mg in both parts of the study.[23] At the end of the second part of the trial, WOMAC pain subscale, patient assessment of response to therapy and investigator assessment of disease status scores were similar in etoricoxib 30, 60 or 90 mg/day and diclofenac 150 mg/day recipients.

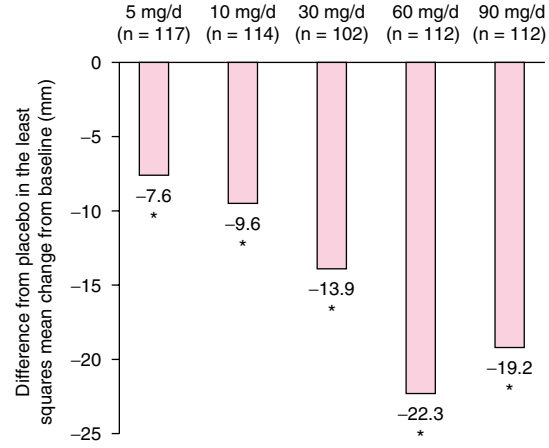


Fig. 3. Effect of etoricoxib on pain control in patients with osteoarthritis of the knee.[23] Difference between etoricoxib and placebo in the least squares mean change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index pain subscale scores. 617 patients were randomised to receive placebo or etoricoxib 5 to 90 mg/day for 6 weeks in a double-blind, multicentre study. * $p < 0.05$.

• Etoricoxib was as effective as naproxen in patients with osteoarthritis, according to the results of the first study comparing these two drugs.[24] After 12 weeks' therapy, significantly greater improvements ($p < 0.001$) from baseline in WOMAC pain and physical function subscale scores and the patient global assessment of disease status score were seen in etoricoxib and naproxen recipients than in placebo recipients (figure 4).

• Three key secondary endpoints were also assessed.[24] A significantly greater reduction ($p < 0.001$) in WOMAC stiffness subscale scores was seen in etoricoxib and naproxen recipients compared with placebo recipients (–24.37 and –23.41 *vs* –14.94mm). In addition, patient global assessment of response to therapy (1.78 and 1.85 *vs* 2.40) and changes in investigator global assessment of disease status (–1.35 and –1.32 *vs* –0.81) significantly favoured etoricoxib and naproxen recipients ($p < 0.001$ *vs* placebo). These latter two end-

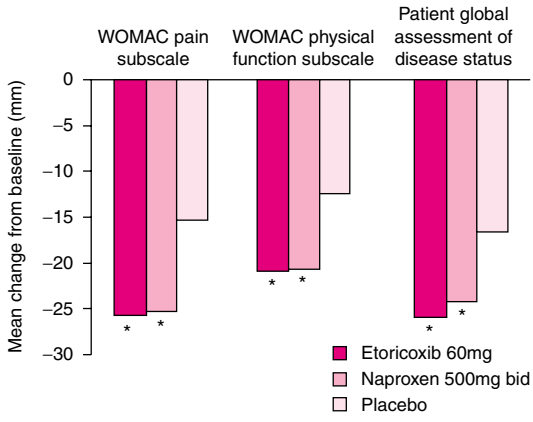


Fig. 4. Effect of etoricoxib in patients with osteoarthritis of the hip or knee. Improvement from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscale scores and patient global assessment of disease status scores (all assessed using 100mm visual analogue scales). Patients were randomised to receive etoricoxib 60mg od (n = 224), naproxen 500mg bid (n = 221) or placebo (n = 56) for 12 weeks in a randomised, double-blind, multicentre study. **bid** = twice daily; **od** = once daily; * $p < 0.001$ *vs* placebo.[24]

points were assessed using a 5-point Likert scale on which lower values represent a better outcome.

• In the second study comparing etoricoxib with naproxen,[22] recipients of these drugs reported significantly greater improvement from baseline in WOMAC pain and physical function subscale scores and the patient global assessment of disease status score than placebo recipients (p values not stated). These improvements were sustained over 1 year of treatment. No quantitative data were reported in the abstract.

• Combined analysis of data from the two studies[22,24] comparing etoricoxib with naproxen revealed that etoricoxib had a rapid onset of effect in patients with osteoarthritis.[35] According to the patient global assessment of response to therapy, onset of effect was seen as early as 4 hours after drug administration on day 1 in etoricoxib recipients ($p = 0.017$ *vs* placebo). In addition, a significantly greater reduction in the WOMAC score for pain while walking on a flat surface was seen in etoricoxib compared with placebo recipients ($p = 0.001$) 4 hours after drug administration on day 2 (this endpoint was not assessed on day 1). Moreover, the beneficial effects associated with etoricoxib therapy were sustained over the 24 hours following drug administration.[35]

• Etoricoxib appears to provide overall symptomatic relief in patients with osteoarthritis.[34] Of the 997 patients in the combined analysis, 24.0% had osteoarthritis of the thumb and 34.6% had osteoarthritis of the interphalangeal joint of the hand. The effects of etoricoxib were similar in these patients to those seen in patients without osteoarthritis of the hand. Moreover, in one of the studies, the improvements in Australian/Canadian Osteoarthritis Hand Index (AUSCAN) subscale scores were significantly greater in patients with osteoarthritis of the hand who received etoricoxib or naproxen than in those who received placebo ($p < 0.05$).

• Significantly greater improvements ($p \leq 0.05$) in the majority of items comprising the social functioning, role-emotional and vitality subscales[38] and the physical functioning and role-physical subscales[36] (assessed using the SF-36 Health Survey) were seen in recipients of etoricoxib and naproxen than in placebo recipients. In addition, greater improvements in the ability to perform daily activities (assessed using the WOMAC physical functioning subscale) were seen in recipients of active treatment than in placebo recipients.[37]

In Patients with Postoperative Dental Pain

The efficacy of etoricoxib in the treatment of postoperative dental pain was studied in two double-blind, single-dose, placebo-controlled trials.[25,26] Patients in both studies had moderate-to-severe pain after the surgical removal of at least two third molars. In a dose-ranging study, 398 patients were randomised to receive single doses of etoricoxib 60, 120, 180 or 240mg, ibuprofen 400mg or placebo.[25] An active-comparator study randomised 200 men and women to receive single doses of etoricoxib 120mg, naproxen sodium 550mg, paracetamol/codeine 600/60mg or placebo.[26] The pri-

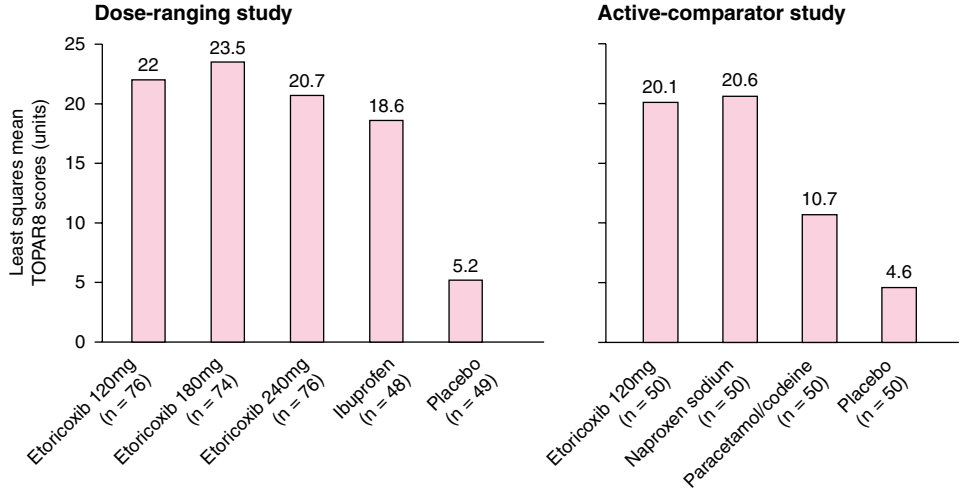


Fig. 5. Total pain relief score over 8 hours (TOPAR8) in patients with moderate-to-severe postoperative dental pain due to extraction of at least two third molars. The dose-ranging study was conducted in 398 patients randomised to single-dose etoricoxib 60, 120, 180 or 240mg, ibuprofen 400mg or placebo (the TOPAR8 score for recipients of etoricoxib 60mg was not reported).[25] The active-comparator trial was undertaken in 200 patients randomised to single-dose etoricoxib 120mg, naproxen sodium 550mg, paracetamol (acetaminophen)/codeine 600/60mg or placebo.[26]

mary endpoint in both studies was the total pain relief score over 8 hours (TOPAR8). Pain intensity and pain relief were both assessed at regular intervals in both studies.

• In the dose-ranging study, etoricoxib 120mg was the smallest dose that provided maximum efficacy, with the 120, 180 and 240mg doses all associated with similar least squares mean TOPAR8 scores that were higher than that for placebo.[25] Ibuprofen was also effective in maximising TOPAR8 scores (see figure 5).

• Etoricoxib was associated with a rapid onset and a long duration of pain relief in patients with postoperative dental pain. The time to confirmed perceptible pain relief was slightly shorter in patients receiving etoricoxib 120mg (≈24 minutes) than in patients receiving ibuprofen (30 minutes) or etoricoxib 60mg (30 minutes). Placebo did not have a measurable time of onset of pain relief. The duration of action, as assessed by the median time to the use of rescue medication, was significantly longer with etoricoxib 120, 180 or 240mg (>24 hours) than with ibuprofen (≈10 hours) or etoricoxib 60mg (≈12 hours) [p values not stated].[25]

• Etoricoxib and naproxen sodium were associated with higher least squares mean TOPAR8 scores than paracetamol/codeine or placebo (20.1 and 20.6 *vs* 10.7 and 4.6 units, respectively; p values not stated) [see figure 5].[26] Time to confirmed perceptible pain relief was similar with the three active treatments (≈30 minutes).[26] Etoricoxib was associated with the longest duration of effect (>24 hours), followed by naproxen sodium (≈22 hours), paracetamol/codeine (≈5.2 hours) and placebo (2 hours).[26]

In Patients with Chronic Low Back Pain

Two 3-month, placebo-controlled trials examined the efficacy of etoricoxib in chronic low back pain;[27,28] the average duration of pain was 12[27] and >11 years.[28] Patients were randomised to receive etoricoxib 60 mg/day (n = 109[27] or 103[28]) or 90 mg/day (n = 106[27] or 107[28]) or placebo (n = 110[27] or 109[28]) for 12 weeks. The primary endpoint in both studies was the improvement from baseline to week 4 in the time-weighted average Low Back Pain Intensity Scale score (assessed

using a 100mm VAS). Combined analyses[39,40] of these two trials[27,28] have also been conducted.

• Etoricoxib provided pain relief in patients (aged 19 to 78 years) with chronic low back pain in the first 3-month trial.[27] After 4 weeks' therapy, significantly greater ($p < 0.001$) reductions in pain were seen in etoricoxib 60 and 90 mg/day recipients compared with placebo recipients (–34.4 and –32.3 *vs* –19.3mm, respectively).[27] This improvement was maintained throughout the trial; at 3 months, pain scores were reduced from baseline by –35.1, –35.7 and –23.0mm in the corresponding treatment groups ($p < 0.001$ for both etoricoxib dosages *vs* placebo).

• Significant improvements in pain intensity scores were seen in etoricoxib compared with placebo recipients after 4 and 12 weeks' therapy in the second 3-month study (p values not stated).[28] In addition, Roland-Morris Disability Questionnaire scores (a measure of functional status) were significantly improved in etoricoxib recipients (p values not stated).

• Etoricoxib improved functional status in patients with chronic low back pain, according to a pooled analysis of the two 3-month trials.[39] After 12 weeks' treatment, a significantly greater ($p < 0.001$) improvement in the Roland-Morris Disability Questionnaire score (a secondary endpoint) was seen in etoricoxib 60 and 90 mg/day recipients than in placebo recipients (–6.85 and –6.43 *vs* –4.21). A significant between-group difference in this parameter was observed after 1 week.

• Further analysis of these two trials revealed a significant improvement in the physical component of the SF-12 Health Survey in patients with chronic low back pain who received etoricoxib.[40] Significantly greater improvements in the physical component score were seen in recipients of etoricoxib 60 mg/day ($p = 0.008$) and 90 mg/day ($p < 0.001$), compared with placebo, after 12 weeks' therapy (8.35 and 8.83 *vs* 6.04). No significant change in the mental component score was seen in any of the treatment groups.

In Patients with Acute Gout

• Etoricoxib 120 mg/day had similar efficacy to indomethacin in patients with acute gout of ≤48 hours duration.[29] In a multicentre double-blind study, patients were randomised to receive etoricoxib 120mg once daily (n = 75) or indomethacin 50mg three times daily (n = 75) for 8 days. The primary endpoint was the change from baseline in patient assessment of pain in the affected joint over days 2 to 5 of the study (scored using the 5-point Likert scale).[29] The least squares mean difference between etoricoxib and indomethacin recipients in the reduction from baseline in joint pain was 0.11 units [95% confidence interval (CI) –0.14 to 0.35] and 0.09 units (95% CI –0.14 to 0.33) over days 2 to 5 and days 2 to 8, respectively. The treatments were considered comparable according to prespecified criteria (95% CI of ±0.5).

• Similarly, comparable improvements in the secondary endpoints (investigator assessment of joint tenderness, swelling and erythema and patient and investigator global assessments of response to treatment) were seen in etoricoxib and indomethacin recipients.[29]

In Patients with Primary Dysmenorrhoea

• Etoricoxib had similar efficacy to naproxen sodium in women with moderate to severe primary dysmenorrhoea in a randomised double-blind crossover study.[30] Seventy-three women (aged 19 to 45 years) received single doses of etoricoxib 120mg, naproxen sodium 550mg and placebo. Least squares mean TOPAR8 scores (the primary endpoint) were significantly greater ($p < 0.001$) with etoricoxib and naproxen sodium administration, compared with placebo administration (20.0 and 21.5 *vs* 12.6 units, respectively).

• The peak analgesic effect was significantly greater ($p < 0.001$) with etoricoxib and naproxen sodium than with placebo administration, with least squares mean peak pain relief scores of 3.4, 3.6 and 2.5 units, respectively.[30] Additional analgesics were required by 13.4, 19.4 and 44% of patients, respectively. With etoricoxib administra-

tion, the median time to rescue medication being required was >24 hours.

In Patients with Haemophilic Arthropathy

• Etoricoxib improved the signs and symptoms of painful haemophilic arthropathy in a multicentre, double-blind study in 102 patients.[31] Patients were randomised to receive etoricoxib 90 mg/day (n = 51) or placebo (n = 51) for 6 weeks. Etoricoxib was significantly more effective than placebo ($p < 0.001$) in improving patient assessment of arthropathy pain scores (the primary endpoint); there was a mean difference between etoricoxib and placebo recipients in the improvement in pain score of –19.44mm using a 100mm VAS.

• Significant improvements in secondary endpoint scores (patient global assessment of arthropathy disease status, patient and investigator global response to therapy, investigator global assessment of arthropathy disease status and WOMAC pain, physical function and stiffness scales) were also reported with etoricoxib therapy compared with placebo (p values not stated). Rescue medication use was numerically less frequent in patients who received etoricoxib compared with placebo, although this was not statistically significant. Etoricoxib was also associated with fewer withdrawals because of lack of efficacy compared with placebo (11.8 *vs* 29.4%; $p = 0.048$).[31]

4. Tolerability

• Etoricoxib was generally well tolerated in clinical studies in patients with rheumatoid arthritis, osteoarthritis, postoperative dental pain, chronic low back pain, acute gout, primary dysmenorrhoea and haemophilic arthropathy.[19-31]

• In patients with rheumatoid arthritis (n = 581) receiving etoricoxib 60 to 120 mg/day or placebo, the most commonly occurring adverse events were headache, diarrhoea, upper respiratory tract infection and nausea (the between-group differences were not statistically significant) [see figure 6].[19] The number of patients with rheumatoid arthritis withdrawing from the 8-week study because of ad-

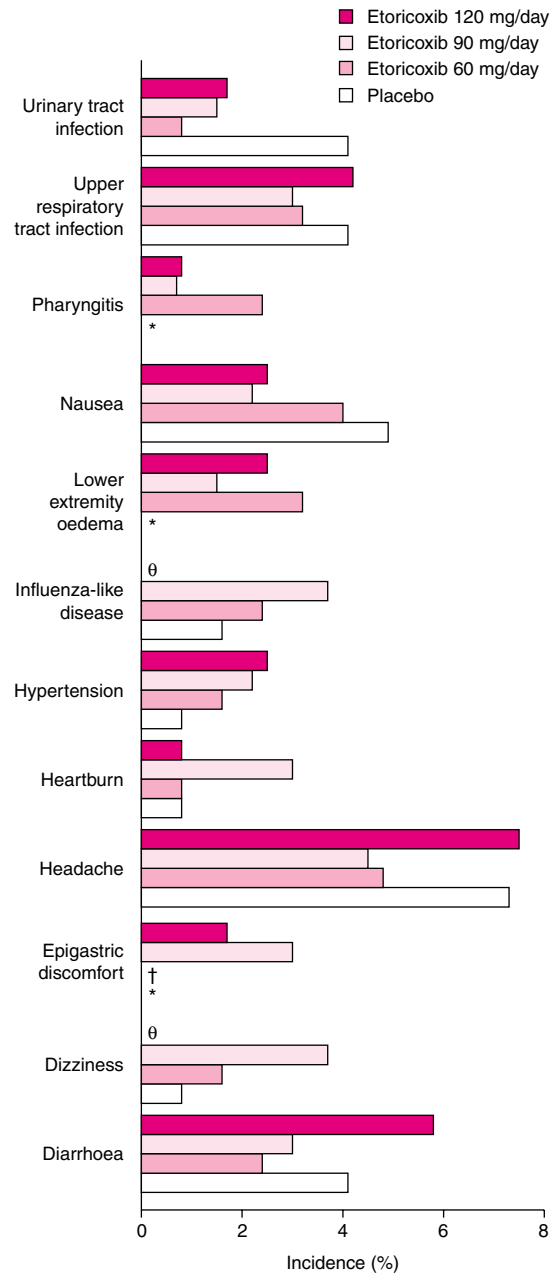


Fig. 6. Adverse events (incidence ≥3% in a single treatment group) in 581 patients with rheumatoid arthritis who received etoricoxib 60 to 120 mg/day or placebo for 8 weeks.[19] Incidence of 0% in placebo recipients (*), etoricoxib 120 mg/day recipients (θ) or etoricoxib 60 mg/day recipients (†).

verse events was similar (≤5%) for placebo and etoricoxib recipients.[19]

• Etoricoxib was well tolerated in a 12-week study in patients with osteoarthritis of the hip or knee (n = 501) who were randomised to receive etoricoxib 60mg once daily, naproxen 500mg twice daily or placebo.[24] The incidence of drug-related adverse events (31.2 *vs* 25.4%) and the proportion of patients who discontinued treatment because of adverse events (10.9 *vs* 2.2%) was higher in naproxen than in etoricoxib recipients.

• The incidence of lower extremity oedema and hypertension was similar in etoricoxib recipients to that seen in naproxen and ibuprofen recipients, according to a pooled analysis of data from studies including patients receiving etoricoxib 60 mg/day (n = 658), 90 mg/day (n = 889) or 120 mg/day (n = 472), naproxen 1 g/day (n = 1034), ibuprofen 2.4 g/day (n = 226) or placebo (n = 1491).[41] The incidence of lower extremity oedema was 3.2, 1.5, 1.3, 2.3, 1.8 and 1.9% in the corresponding treatment groups; hypertension occurred in 4.0, 3.4, 4.7, 2.9, 6.6 and 2.0% of patients. Discontinuations occurred in 0 to 0.4% of patients because of lower extremity oedema or because of hypertension.

• In the pooled analysis,[41] the proportion of patients receiving etoricoxib 60, 90 or 120 mg/day, naproxen 1 g/day, ibuprofen 2.4 g/day or placebo who developed elevated serum creatinine levels was 0.8, 0.7, 0.2, 0.7, 0 and 0.3%, respectively. No patient discontinued treatment because of elevated serum creatinine levels.

Gastrointestinal Tolerability

• The incidence of investigator-reported upper GI perforations, ulcers and bleeds (PUBs) with etoricoxib was less than half that associated with traditional non-COX-selective NSAIDs in a combined analysis of data from ten clinical trials.[42] Patients with rheumatoid arthritis, osteoarthritis or chronic low back pain were treated with once-daily etoricoxib 60 to 120mg (n = 3142) or a traditional non-COX-selective NSAID (diclofenac 150 mg/day, ibuprofen 2.4 g/day or naproxen 1 g/day; n = 1828) in these studies.

• Eighty-one PUBs were reported by investigators and 71 were confirmed (PUBs were confirmed by an external, blinded committee using prespecified criteria).[42] For etoricoxib versus traditional NSAIDs, the relative risk (RR) of an investigator-reported PUB was 0.47 (95% CI 0.30 to 0.74; p = 0.001) and of a confirmed PUB was 0.44 (95% CI 0.27 to 0.72; p < 0.001).[42]

• Etoricoxib was associated with fewer treatment discontinuations because of NSAID-type GI symptoms compared with traditional non-COX-selective NSAIDs. NSAID-type GI symptoms, defined as acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea and abdominal pain, were assessed in a group of 4028 patients with rheumatoid arthritis, osteoarthritis or chronic low back pain who had participated in randomised double-blind trials.[43,44] Patients received once-daily etoricoxib 60 to 120 mg/day (n = 2670), diclofenac 150 mg/ day (n = 232) or naproxen 1 g/day (n = 1126).

• For etoricoxib versus traditional NSAIDs, the RR for discontinuation because of NSAID-type GI symptoms was 0.59 (95% CI 0.39 to 0.87; p = 0.009) and the RR for treatment discontinuation because of any GI symptom, including abdominal pain, was 0.55 (95% CI 0.42 to 0.71; p < 0.001).[43,44]

• Another analysis of this same dataset (n = 4028)[45] found that etoricoxib recipients were significantly less likely (p < 0.001) than non-COX-selective NSAID recipients to use gastroprotective agents (RR 0.61; 95% CI 0.49 to 0.76) or GI comedications (RR 0.61; 95% CI 0.51 to 0.74). Gastroprotective agents included H_2-receptor antagonists, proton pump inhibitors, prostaglandins and sucralfate, and GI comedications included gastroprotective agents, antacids, antispasmodics, antiflatulents and antiregurgitants.

• Discontinuation rates were also assessed in a combined analysis of data from randomised, double-blind studies with placebo-controlled treatment periods; 2151 etoricoxib 60 to 120 mg/day

recipients, 790 naproxen 1 g/day recipients and 1194 placebo recipients were included.[43,44] The risk of discontinuation because of NSAID-type GI symptoms was significantly higher in naproxen versus placebo recipients (RR 3.56; 95% CI 1.38 to 9.16; p = 0.009), but not in etoricoxib recipients (RR 1.44; 95% CI 0.61 to 3.39; p = 0.407). Similarly, compared with placebo recipients, the risk of discontinuation because of any GI symptom including abdominal pain was significantly higher in naproxen recipients (RR 3.63; 95% CI 1.78 to 7.43; p < 0.001), but not in etoricoxib recipients (RR 1.36; 95% CI 0.72 to 2.56; p = 0.338).

• Another analysis of this same dataset (n = 4135)[45] found that the use of gastroprotective agents was significantly higher in naproxen versus placebo recipients (RR 2.84; 95% CI 1.59 to 5.09; p < 0.001), but not in etoricoxib recipients (RR 1.38; 95% CI 0.82 to 2.33; p = 0.221). Similarly, use of GI comedications was significantly higher in naproxen versus placebo recipients (RR 2.86; 95% CI 1.74 to 4.72; p < 0.001), but not in etoricoxib recipients (RR 1.33; 95% CI 0.85 to 2.09; p = 0.210).

5. Dosage and Administration

The recommended dosage of etoricoxib is 60 mg/day for osteoarthritis or chronic musculoskeletal pain, 60 or 120 mg/day for primary dysmenorrhoea, 90 mg/day for rheumatoid arthritis and 120 mg/day for acute gouty arthritis or acute pain associated with dental surgery.[12]

6. Etoricoxib: Current Status

Etoricoxib is a COX-2-selective NSAID that has been approved for a number of indications in several countries worldwide (e.g. the UK and some Latin American countries). Indications include the treatment of osteoarthritis, rheumatoid arthritis, gouty arthritis, chronic musculoskeletal pain (including chronic low back pain), postoperative dental pain and primary dysmenorrhoea.

The efficacy of etoricoxib in the treatment of rheumatoid arthritis, osteoarthritis, postoperative dental pain, chronic low back pain, acute gout, primary dysmenorrhoea and haemophilic arthropathy has been demonstrated in well designed studies. Etoricoxib was generally well tolerated and had better GI tolerability than conventional non-COX-selective NSAIDs.

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Correspondence: *Deborah J. Cochrane*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz